REMARKS

Reconsideration of this application is respectfully requested.

Claims 91-150 were previously pending in this application. New replacement claim 91 has been entered above. Claim 150 has been allowed. New claims 151-168 have been added. Claims 142-149 have been canceled. Accordingly, claims 91-141 and 150-168 are presented for further examination in this application.

I. Claim Changes

The following changes to the claims have been effected by this paper.

In replacement claim 91, Applicants have inserted the phrase "independent of a requirement for the introduction of an endonuclease." By so doing, the process in claim 91 is now independent of two requirements. First, the process is independent of a requirement for introducing an intermediate structure for the production of the specific nucleic acid. Second, the process is independent of the aforementioned introduction of an endonuclease.

As required under Simplified Amendment Practice. Replacement paragraphs/sections/claims to be used. 37 CFR 1.121, and as set forth in the Changes to the Patent Rules (37 CFR 1.121 MPEP Bookmark, Volume 1, Issue 3), a marked-up version of claim 91 amended above is attached as Exhibit A. This marked-up version is entitled "Marked-Up Version Of Amended Claims."

In new claims 151-168, Applicants are seeking to pursue subject matter commensurate with their broad and complete disclosure. With respect to claims 151-157, these depend directly or ultimately from allowed claim 150. Claim 151 recites "wherein said protein-nucleic acid construct comprises a double-stranded nucleic acid." Claim 152 recites "wherein said sequence coding for a protein

comprises a sequence for said RNA polymerase." In claim 153, the "sequence coding for a protein comprises a sequence for said RNA polymerase." Claim 154 combines the limitations of claims 152 and 153, this claim reciting "wherein said sequence coding for a protein comprises a sequence for said RNA polymerase and a sequence for a protein other than said RNA polymerase."

Claims 155-157 are directed to related subject matter. Claim 155 recites "wherein said sequence coding for a protein comprises a sequence for a second RNA polymerase that is different from said RNA polymerase in said construct." In claim 156, the process is defined as "further comprising a second promoter for said second RNA polymerase." In claim 157, the process further comprises "a sequence for a protein, wherein said protein is transcribed from said second promoter."

New claim 158 is independent and is directed to an *in vivo* process for producing a specific nucleic acid. In this claim, two process steps are recited. The first steps comprises "providing a conjugate which is capable of producing a specific nucleic acid when present in a cell, said conjugate comprising a protein-nucleic acid construct." The construct comprises three elements: (i) at least one promoter; (ii) at least one segment of said specific nucleic acid comprising a template for transcription; and (iii) an RNA polymerase. The second step in claim 158 calls for (b) introducing said conjugate into a cell, thereby producing said specific nucleic acid.

Claims 159-166 depend ultimately from claim 158. Claim 159 recites "wherein said specific nucleic acid being produced comprises sense RNA or antisense RNA." In claim 160, the "sense RNA codes for a protein." Claims 161-164 define the protein coding sense RNA. Thus, the protein coding sense RNA "codes for said RNA polymerase (claim 161); "codes for a protein other than said

RNA polymerase (claim 162); "codes for said RNA polymerase and a protein other than said RNA polymerase" (claim 163); and "comprises a sequence for a second RNA polymerase that is different from said RNA polymerase in said construct (claim 164).

New claims 165 and 166 further comprise additional elements. In claim 165, the process of claim 164 is defined as "further comprising a second promoter for said second RNA polymerase." Claim 166 depends from claim 165 and further comprises "a sequence for a protein, wherein said protein is transcribed from said second promoter."

New claim 167 is also independent and is directed to an *in vivo* process for producing a specific nucleic acid. The process of this claim comprises two steps. In the first step (a) a conjugate is provided that comprises a protein-nucleic acid construct. The conjugate is capable of producing a nucleic acid when present in a cell, and the construct comprises at least one complementary sequence to a primer present in the cell. In the second step (b), the conjugate is introduced into a cell, thereby producing the specific nucleic acid. Claim 168 depends from claim 167 and it recites that "said polymerase comprises a DNA polymerase or reverse transcriptase."

All of the above claim changes, including replacement claim 91 and the new claims, are believed to be supported by Applicants' original disclosure. Entry of the foregoing replacement claim and new claims 151-168 is respectfully requested.

II. Priority Filing Date

Applicants appreciate the Examiner's statement that they are entitled to the priority filing date of the immediate parent application, U.S. Patent Application Serial No. 08/182,621, filed on January 13, 1994.

Before turning to the substantive issues in the Office Action, Applicants acknowledge, with appreciation, the withdrawal of two art-based rejections based separately upon the Romano and Gerdes publications.

The First Rejection Under 35 U.S.C. §102

Claims 91-96 and 99-120 stand rejected under 35 U.S.C. §102(e) as anticipated by Walker, U.S. Patent No. 5,455,166, issued on October 3, 1995. In the Office Action (pages 2-5), the Examiner stated:

> Walker et al teaches an in vitro process for producing more than one copy of a specific nucleic acid, the process being independent of a requirement for the introduction of an intermediate structure for the production of the specific nucleic acid, (Abstract, Figures 1 and 2), the process comprising the steps of:
>
> (a) providing a nucleic acid sample containing or suspected of containing the sequence of the specific nucleic acid (Example 1, column 10, lines 58-63 and Example 2, column 11, line 63 and Example 3, column 12, lines 49-53);
>
> (b) contacting the sample with a mixture comprising:
>
> (i) nucleic acid precursors (Figure 1)
>
> (ii) one or more specific nucleic acid primers each of which is complementary to a distinct sequence of the specific nucleic acid (Figure 1 and Example 2, column 11, lines 56-58), and
>
> (iii) an effective amount of a nucleic acid producing catalyst (Example 1, column 11, lines 1-7); and
>
> (c) allowing the mixture to react under isostatic conditions, temperature, buffer and ionic strength, thereby producing more than one copy of the specific nucleic acid (Figures 1 and 2 and Examples I2, column 12, lines 3-6).
>
> Walker teaches the process wherein the nucleic acid is single stranded or double-stranded DNA (Figures 1 and 2 and Examples 1 and 2).
>
> Walker teaches the process wherein the nucleic acid is in solution (Example 2, column 11, lines 56-62).

Walker teaches the process further comprising the steps of treating the specific nucleic acid with a restriction enzyme capable of producing blunt ends (Figures 1 and 2, column 8, lines 20-60 and example 1, column 11, line 5 and example 2, column 12, line 5).

Walker teaches the process wherein the nucleic acid is isolated or purified prior to the contracting step or the reacting step (Example 3, column 12, lines 49-52).

Walker teaches the process wherein the releasing step is carried out by means of a restriction enzyme (Figures 1 and 2).

Walker teaches the process wherein the nucleic acid precursors are selected from nucleoside triphosphates and nucleoside triphosphate analogs, or a combination thereof (column 8, lines 20-60 and Example 3, column 12, line 58).

Walker teaches the process wherein the nucleic acid precursors are selected from ATP, GTP, CTP, UTP, or TTP (Figures 1 and 2 and Example 2, column 12, lines 1-3).

Walker teaches the process wherein the nucleoside triphosphates analogs are naturally occurring or synthetic, or a combination thereof (Figures 1 and 2 and Example 2, column 12, lines 1-3).

Walker teaches the process wherein at least one of the nucleoside triphosphate analogs is modified on the phosphate (column 8, lines 20-60 and Example 3, column 12, line 58).

Walker teaches the process wherein the specific nucleic acid primers contains a 3'-hydroxyl group or an isosteric configuration of heteroatoms containing sulfur (Figures 1 and 2 and Example 2, column 11, lines 56-57)

Walker teaches the process wherein the specific nucleic acid primers are substantially complementary to one another and does not contain more the five complementary to base-pairs in the sequences therein (Column 15, SEQ ID Nos; 5 and 6).

Walker teaches the process wherein the specific nucleic acid producing catalyst is selected from DNA polymerase (Example 1, column 11, lines 1-5).

Walker teaches the process further comprising the step of detecting the product by means of incorporating into the product a labeled primer (Example 3, column 12, line 65 to column 13, line 13 and Table III).

> Walker teaches the process further comprising the step of regenerating the one or more specific nucleic acid primers for additional production processes (Figures 1 and 2).

On page 10 in the Office Action, the Examiner further stated:

> 10. In response to applicant's argument that the Walker reference fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., intermediate structure that is not normally present in the specific target nucleic acid) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The first anticipation rejection is respectfully traversed.

As indicated in the opening remarks of this paper, claim 91 has been amended to now recite that the process is "independent of a requirement for the introduction of an endonuclease." In light of the language now present in claim 91, it is believed that the anticipation rejection based on Walker's patent has been rendered moot and irrelevant.

Reconsideration and withdrawal of the first anticipation rejection is respectfully requested.

The Second Rejection Under 35 U.S.C. §102

Claims 142, 144, 146 and 147 stand rejected under 35 U.S.C. 102(b) as anticipated by Zaichikov et al. [Bioorganicheskaia Khimia 14(1):121-124 (1988)]. In the Office Action (page 5), the Examiner stated:

> Zaichikov et al teaches a conjugate comprising a protein-nucleic acid construct, the nucleic acid construct not coding for said protein, and which conjugate produces a nucleic acid when present in a cell (Abstract, lines 1-3).

> Zaichikov et al. teaches a conjugate wherein the protein comprises an RNA polymerase or a subunit thereof (Abstract, lines 1-6).

The second anticipation rejection based on Zaichikov et al. is believed to have been rendered moot by the cancellation of claims 142-149.

Withdrawal of the second anticipation rejection is respectfully requested.

The Third Rejection Under 35 U.S.C. §102

Claims 142-148 stand rejected under 35 U.S.C. 102(b) as anticipated by Knorre et al. [IZV SIB OTD AKAD NAUK SSSR SER BIOL NAUK 0(2):98-104 (1989)]. In the Office Action (page 6), the Examiner stated:

> Knorre et al. teaches an in vivo process for producing a specific nucleic acid, the process comprising a protein-nucleic acid construct, the nucleic acid construct not coding for said protein, and which conjugate produces a nucleic acid when present in a cell (Abstract, lines 1-19).
>
> Knorre et al. teaches a conjugate wherein the protein comprises an RNA polymerase or a subunit thereof (Abstract, lines 1-6) and the nucleic acid construct contains the corresponding RNA polymerase promoter (Abstract, lines 1-8).

The third anticipation rejection based on Knorre et al. is also believed to have been rendered moot by the cancellation of claim 142-149.

Withdrawal of the third anticipation rejection is respectfully requested.

Commonality of Ownership

Applicants assert that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made.

The First Rejection Under 35 U.S.C. §103

Claims 91-120 stand rejected under 35U.S.C. §103(a) as being unpatentable over Walker, U.S. Patent No. 5,455,166, issued on October 3, 1995, cited *supra*., in view of Matthews et al. [Analytical Biochemistry 169:1-25 (1988)].

In the Office Action (page 7), the Examiner stated:

> Walker teaches the processes of claims 91-96 and 99-120 as described above.
>
> Walker does not teach the isolation or purification of the specific nucleic acid by means of sandwich hybridization or capture sandwich hybridization or capture sandwich hybridization.
>
> Matthews et al teaches the isolation or purification of the specific nucleic acid by means of sandwich hybridization or capture sandwich hybridization (Figures 9, 10, 12, 13 and 14).
>
> It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to substitute sandwich hybridization model of Matthews et al. in the method of Walker, since Matthews et al states, "The sandwich hybridization strategy is not limited to quantitation of a nucleic acid species, but can easily be applied to detection of altered restriction sites in DNA, providing the exact mutation to be detected is known (page 16, column 1, lines 7-11)." An ordinary practitioner would have been motivated to combine the sandwich hybridization model of Matthews et al. in the method of Walker, in order to achieve the express advantages noted by Matthews et al. of a method which provides easy application to detection of altered restriction sites in DNA.

The first obviousness rejection is respectfully traversed.

As indicated above, claim 91 has been amended to recite that the process is independent of a requirement for the introduction of an endonuclease. Claims 92-120 are directly or ultimately dependent from amended claim 91. Thus, each of these claims is believed to be patentably distinct from Walker's patent disclosure. Even the addition of Matthews et al. does not cure the deficiency in Walker's disclosure regarding the requirement for an endonuclease.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the first obviousness rejection based upon Walker in view of Matthews et al.

The Second Rejection Under 35 U.S.C. §103

Claims 91-96 and 99-136 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Walker, U.S. Patent No. 5,455,166, issued on October 3, 1995, cited *supra.*, in view of Pardee et al., U.S. Patent No. 5,455,166. In the Office Action (page 8), the Examiner stated:

> Walker teaches the processes of claims 91-96 and 99-120 as described above.
>
> Walker does not teach primers comprising at least one ribonucleic acid segment.
>
> Walker does not teach removing of primer-coded sequences from the product by digestion with an enzyme ribonuclease H.
>
> Pardee et al. teaches primers comprising at least one ribonucleic acid cell segment (Column 1, line 66 to Column 2, line 7).
>
> Pardee et al. teaches removing of primer-coded sequences from the product by digestion with an enzyme ribonuclease H (Column 1, line 66, to Column 2, line 7).
>
> Walker does not teach one or more specific chemically-modified primers each of which primer is substantially complementary to a distinct sequence of the specific nucleic acid.
>
> Pardee et al. teaches one or more specifically chemically-modified primers each of which is substantially complementary to a distinct sequence of the specific nucleic acid (Column 1, line 66 to Column 2, line 7).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the chemically-modified primers made by RNase H of Pardee et al. in view of Walker, since Pardee et al. state, "This reaction is very efficient (Column 2, lines 5-6). "By employing scientific reasoning, an ordinary practititioner would have been motivated to substitute and combine the chemically-modified primers made by RNase H of Pardee et al. in the method of Walker, in order to produce more than one copy of a specific nucleic acid and also in order to

achieve the express advantages, as noted by Pardee et al., of a reaction which is very efficient.

The second obviousness rejection based upon Walker in view of Pardee et al. is respectfully traversed.

The passages in Pardee et al. cited in the instant rejection include Column 1, line 66 to column 2, line 7. These passages are in the context of synthesizing a second strand of cDNA (Column 1 lines 61-64). In summary, a strand of RNA is the initial target, and a first cDNA copy of this RNA target is made thereby resulting in a double-stranded molecule that comprises one strand of RNA and one strand of DNA. The double-stranded molecules are treated with RNase H which will randomly produce nicks and gaps at various sites in the original RNA template. The remaining RNA target thereby has 3′ ends which can be used as primers to create a 2nd cDNA strand.

In response to Pardee's cited disclosure that is paraphrased above, Applicants offer the following points.

1) Unlike the presently claimed invention, there is **no description of** "removal of primer coded sequences from the product" in the art described by Pardee et al. There are no primer coded sequences in Pardee's initial RNA target. Instead, the removal step using RNase H is responsible for the generation of Pardee's primers. In a certain sense, the primer coded sequences in Pardee et al. are the portions that were **not** removed, i.e., the remaining RNA fragments.

2) Instant claims 121, 129 and 137 refer to "contacting said sample with a mixture comprising.....one or more specific primers comprising at least one ribonucleic acid segment....." This claim language is distinguished from Pardee et al. who disclose a process where the sample is actually the source of the

ribonucleic acid primers. As such, there is no contacting step in Pardee et al. between the sample and ribonucleic primers, unlike the present invention.

3) Instant claims 121, 129 and 137 refer to "one or more **specific** primers comprising at least one ribonucleic acid segment....." . As noted above, the primers generated from the RNase digestion (in the method described by Pardee et al.) are of a random nature that can have a variety of sites for 3′ and 5′ ends. Unlike the present invention that calls for specific primers, Pardee et al. would generate -- at best -- random primers at random sites that are base paired with their cDNA copies.

4) Instant claims 121, 129 and 137 refer to "...removing substantially or all primer-coded sequences from the product produced in (c) to regenerate a primer binding site, thereby allowing a new priming event to occur....". Regeneration of a primer binding site has no applicability or relevance to Pardee's disclosure since there is no primer available to bind at that site in Pardee et al.

5) In the rejection, Pardee et al. is characterized as teaching "one or more chemically modified primers." In response, Applicants note that the only time structural features of primers is mentioned in Pardee et al. in column 1, line 66 to column 2, line 7 by Pardee et al., is the passage "leaving a 3′ hydroxyl and a 5′ phosphate." Applicants note that this is a description of enzymatically generating a primer by a cleavage reaction and it would not be generally recognized in the art as having been chemically modified without some additional action being taken. As described by Pardee et al., the primers are normal, unmodified segments of a nucleic acid. Thus, no chemically modified primers are disclosed or suggested in Pardee et al.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the second obviousness rejection.

The Third Rejection Under 35 U.S.C. §103

Claims 91-96, 99-120 and 129-141 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Walker, U.S. Patent 5,455,166, issued on October 3, 1995, cited *supra.*, in view of Pardee et al., cited *supra*, further in view of Courey et al. [Journal of Molecular Biology 202:35-43 (1988)] In the Office Action (pages 89-10), the Examiner stated:

> Walker in view of Gerdes et al.(sic) in view of Pardee et al. teach the processes of claims 91-96, 99-120 and 129-136 as described above.
>
> Walker in view of Pardee et al. do not teach one or more specific unmodified primers each of which primer comprises at least one non-complementary sequence to a distinct sequence of the specific nucleic acid such that upon hybridization to the specific nucleic acid at least one loop structure is formed.
>
> Courey et al teaches one or more specific unmodified primers each of which primer comprises at least one non-complementary sequence to a distinct sequence of the specific nucleic acid such that upon hybridization to the specific nucleic acid at least one loop structure is formed (Figures 2, 5 and 6).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the loop forming supercoiling model of Courey et al. in the method of Walker in view of Pardee et al., since Walker states, "The invention further relates to methods of generating amplified products which can function as probes or templates for sequence analysis (column 4, lines 41-47)." Courey et al provides further motivation as he states, "Lengths of cruciform arms are strongly dependent on sequence imperfections in the palindrome (page 36, column 1, lines 11-14)." An ordinary practitioner would have been motivated to combine the loop forming supercoiling model of Courey et al. in the method of Walker in view of Pardee et al., in order to achieve the express advantages, as noted by Courey et al., of a method that provides the detection of sequence imperfections in a nucleic acid sample.

The third obviousness rejection is respectfully traversed.

With respect to Courey's disclosure, Applicants respectfully point out that this disclosure concerns the effect of sequences in supercoiled DNA and as such, it is irrelevant to Walker or Pardee et al., as well as the present invention. Walker, Pardee et al. and the present invention describe amplicons that are linear, double-stranded pieces of DNA. No supercoiling is disclosed, formed, envisioned or even capable of forming in any of these three disclosures, including the present invention. Thus, the proposed combination of Courey et al. with the other two documents, is not proper. Applicants respectfully request, therefore, that the third obviousness rejection be withdrawn upon further reconsideration, thereby placing all of the pending claims in condition for allowance.

Submission of Art-Related Documents

Applicants are concurrently filing with this paper an Information Disclosure Statement Under 37 C.F.R. §§1.56 and 1.97-1.98. In their IDS attached to this Amendment as Exhibit B, Applicants are submitting 57 documents for consideration by the Examiner and the Patent Office.

Favorable action is respectfully requested.

* * * * * * *

SUMMARY AND CONCLUSIONS

Claims 91-141 and 150-168 are presented for further examination. In addition to claim 91 having been amended, new claims 151-168 have been added above.

The fee for adding new claims 151-168 is $132 based upon ten additional new claims [10 claims X $9 = $90] and one new independent claim [1 claim X $42 = $42]. The Patent and Trademark Office is hereby authorized to charge the amount of $132 to Deposit Account No. 05-1135. No other fee or fees are believed due in connection with this Amendment. In the event that any other fee or fees are due, however, The Patent and Trademark Office is hereby authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

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